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Optimal Control of a Dengue-Dengvaxia Model: Comparison Between Vaccination and Vector Control

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Abstract: Dengue is the most common mosquito-borne viral infection transmitted disease. It is due to the four types of viruses (DENV-1, DENV-2, DENV-3, DENV-4), which transmit through the bite of infected *Aedes aegypti* and *Aedes albopictus* female mosquitoes during the daytime. The first globally commercialized vaccine is Dengvaxia, also known as the CYD-TDV vaccine, manufactured by Sanofi Pasteur. This paper presents a Ross-type epidemic model to describe the vaccine interaction between humans and mosquitoes using an entomological mosquito growth population and constant human population. After establishing the basic reproduction number $\mathcal{R}_0$, we present three control strategies: vaccination, vector control, and the combination of vaccination and vector control. We use Pontryagin's minimum principle to characterize optimal control and apply numerical simulations to determine which strategies best suit each compartment. Results show that vector control requires shorter time applications in minimizing mosquito populations. Whereas vaccinating the primary susceptible human population requires a shorter time compared to the secondary susceptible human.

Keywords: Dengvaxia; Vaccination; $\mathcal{R}_0$; Optimal Control; Pontryagin maximum principle

MSC: 34D23; 92D30; 92-10; 49J15

1 Introduction

Dengue is a mosquito-borne viral infection found in tropical and subtropical regions around the world. It is the most common viral infection transmitted disease. In a study by [4] an estimated 96 million apparent dengue infections globally in 2010 predominantly, 70% in Asia. In the Philippines alone, 271,480 dengue cases were reported nationwide from January 1 to August 31, 2019. [8] It occurs nationally in the Philippines, including urban and peri-urban areas, with peak transmission during the rainy season.

Dengue is a viral infection caused by four types of viruses (DENV-1, DENV-2, DENV-3, DENV-4), which transmit through the bite of infected *Aedes aegypti* and *Aedes albopictus* female mosquitoes during the daytime. In most cases, dengue is a self-limiting illness. However, it may require hospital admission, where supportive care can modify the course of the illness. Infection from one type grants life-long immunity to that virus strain and also appears to grant partial protection against the other types temporarily. That is, when infected for a second time with a different type of virus, a more severe form of the disease will occur, known as Dengue Hemorrhagic Fever (DHF). In the Philippines alone, 1,107 deaths are reported from January 1 to August 31, 2019, due to dengue fever [8].

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Efforts to develop a vaccine against dengue have been ongoing for decades. The first such vaccine to be used commercially is CYD-TDV, marketed as Dengvaxia by Sanofi Pasteur. Dengvaxia was licensed in December 2015 and approved in 11 countries. One such country is the Philippines. On December 1, 2015, the commercial sale of Dengvaxia was approved, making the Philippines the first Asian country to commercialize Dengvaxia [12]. In effect, in April 2016, the Department of Health (DOH) launched the dengue vaccination campaign in the Philippine regions of Central Luzon, Calabarzon, and Metro Manila, involving more than 800,000 school children who received at least one dose of the vaccine. Dengvaxia is a live vaccine of serotypes 1, 2, 3, and 4 [18]. It is a live attenuated chimeric product made using recombinant DNA technology by replacing the PrM (pre-membrane) and E (envelope) structural genes of yellow fever attenuated 17D strain vaccine with those from the four dengue serotypes. It should be administered in three doses of 0.5 mL subcutaneous (SC) six months apart. Sanofi Pasteur recommended that the vaccine only be used in people between the age of 9 to 45 and people already infected by one type of virus [2]. It is because outcomes may be worse in those who have not yet been infected.

Mathematical modeling has been used to test and determine the effectiveness of different intervention strategies in controlling dengue. SEIRS compartmental models accounting for Susceptible, Exposed, Infected, and Removed for the human population, and susceptible and infected for mosquito population were widely promoted. [14] studied a system of differential equations that models the population dynamics of SEIR vector transmission of dengue fever. While [7] proposed a model with two different viruses acting at separated intervals of time. They study the dynamics of dengue fever while concentrating on its progression to the hemorrhagic form to understand the epidemic phenomenon and suggest strategies for the control of the disease. Furthermore, [11] derived and analyzed the model taking into account the severe DHF compartment in the transmission model. They find a control measure to reduce the DHF patients in the population or keep the number of patients at an acceptable level. Also, [1] surveyed a model framework for dengue fever epidemiology. They discuss the role of several subsequent infections versus a detailed number of dengue serotypes included in the model framework and the human immunological aspects associated with disease severity, identifying the implications for model dynamics and their impact on vaccine implementation.

To determine the optimal control in minimizing the spread of dengue fever has also been studied. [17] described the dynamics of dengue disease in the compartment model, taking into account chemical controls and mechanical control applied on the mosquitoes. [13] presented a control mechanism based on a dengue model with vertical transmission considering the two policies, namely vaccination, and insecticide administration. [6] evaluated a control strategy, which aims to eliminate the *Aedes aegypti* mosquito, as well as proposals for the vaccination campaign. Their results show that eradicating dengue fever is done using an immunizing vaccine since control measures against its vector are not enough to stop the disease from spreading. Moreover, [9] designed a new mathematical model to assess the impact of the newly-released Dengvaxia vaccine on the transmission dynamics of two co-circulating dengue strains.

This paper is the first study to take into account the proposal of Sanofi Pasteur. Herein we introduce a new mathematical model of Dengvaxia. As recommended by the World Health Organization [16], vaccination should be given to individuals who have been already infected by one strain virus. In this paper, we split the susceptible human compartment into primary or secondary susceptible humans, that is, individuals who have not been infected and individuals who have been infected by one or more strains of the dengue virus. Then we present a Ross-type epidemic model describing the interaction between humans and the mosquito population. It is the first dengue model that uses the entomological growth function for the mosquito population. We first compare three control strategies concerning the reproduction number: vaccination, vector control, and the combination of the two. Moreover, the optimal control of the three methods is computed to determine the best strategy for the population.

2 The model and its analysis

2.1 Description of model with vaccination

We assumed that dengue viruses are virulent and that no other microorganism attacks the body. The model is based on the Ross-type model. Let H be the human population subdivided into primary susceptible S_h , secondary susceptible $\tilde{S}_h$, infected I_h and removed R_h . Primary susceptible humans are individuals who have not yet been infected by dengue. In contrast, secondary susceptible humans are individuals who previously had dengue infections. Let M be the population of females mosquitoes split into two groups of susceptible S_m and infectious I_m mosquitoes. Figure 1 describes the flow of dengue disease.

Figure 1: Compartmental representation of the dynamics of dengue virus in the human and mosquito population.

Since human have a meager mortality rate compared to mosquitoes, we neglect the natural death of the humans. The following system of ordinary equations governed the dynamics of humans:

$$S'_h(t) = -\frac{ab_h I_m(t)}{H(t)} S_h(t) \quad (1)$$

$$I'_h(t) = \frac{aI_m(t)}{H(t)} (b_h S_h(t) + \tilde{b}_h \tilde{S}_h(t)) - \gamma_h I_h(t) - \delta_h I_h(t) \quad (2)$$

$$\tilde{S}'_h(t) = \gamma_h I_h(t) - \frac{a\tilde{b}_h I_m(t)}{H(t)} \tilde{S}_h(t) \quad (3)$$

$$R'_h(t) = \delta_h I_h(t) \quad (4)$$

while the dynamics of mosquitoes follows:

$$S'_m(t) = -\frac{ab_m I_h(t)}{H(t)} S_m(t) - \mu_m S_m(t) + g(M(t)) \quad (5)$$

$$I'_m(t) = \frac{ab_m I_h(t)}{H(t)} S_m(t) - \mu_m I_m(t). \quad (6)$$

Note that the total population of human is $H = S_h + I_h + \tilde{S}_h + R_h$ and the total population of mosquito is $M = S_m + I_m$. In this work, we consider constant human population, which is $H'(t) = 0$, and an entomological growth function for mosquito population, which is $M'(t) = g(M(t)) - \mu_m M(t) = \alpha_m M(t) e^{-\beta_m M(t)} - \mu_m M(t)$ as in [5], where μ_m is the death rate and α_m is the natural birth rate of the mosquitoes.

The parameters $ab_h I_m \frac{S_h}{H}$ represent the infection rate of the proportion of primary susceptible individuals to be infected with the dengue virus. Wherein b_h is the probability of transmission of the virus from an infected mosquito to a primary susceptible human, and a represents a mosquito's average bites. Moreover, $\tilde{a}\tilde{b}_h I_m \frac{\tilde{S}_h}{H}$ is the infection rate of the proportion of susceptible individuals who had been previously infected with dengue to become infectious again with different serotypes, $\tilde{b}_h$ is the probability of transmission of the virus from an infected mosquito to secondary susceptible human. Furthermore, the rate of susceptible secondary people recovering from infection from one serotype is represented by $\gamma_h I_h(t)$.

For the mosquito compartment, $g(M(t))$ is the growth of the total mosquito population, and $ab_m S_m \frac{I_h}{H}$ is the infection rate of susceptible mosquitoes to be infectious once it bites a ratio of the infected human population. The parameter b_m is the transmission probability from an infected human to a susceptible mosquito.

2.2 Well-posedness and positivity of solution

To simplify the reading, the system of ordinary differential equations is rewritten as $U'(t) = F(t, u(t))$ with

$$U(t) = \left(u_1 = S_h, u_2 = I_h, u_3 = \tilde{S}_h, u_4 = R_h, u_5 = S_m, u_6 = I_m \right)^t$$

and

$$F(U(t), t) = \left(-\frac{ab_h u_6 u_1}{H}, \frac{au_6 (b_h u_1 + \tilde{b}_h u_3)}{H} - \gamma_h u_2 - \delta_h u_2, \gamma_h u_2 - \frac{\tilde{a}\tilde{b}_h u_6 u_3}{H}, \delta_h u_2, -\frac{ab_m u_2 u_5}{H} - \mu_m u_5 + g(M), \frac{ab_m u_2 u_5}{H} - \mu_m u_6 \right)^t.$$

Theorem 2.1. *The domain Ω defined by*

$$\Omega = \left\{ U \in \mathbb{R}_+^6 : 0 \leq u_1 + u_2 + u_3 + u_4 = H_0, 0 \leq u_5 + u_6 \leq \max \left(\frac{\alpha_m}{\beta_m \mu_m}, M_0 \right) \right\}$$

is positively invariant. In particular, for an initial datum $U(0)$ in Ω , there exists a unique global in time solution U in $\mathcal{C}(\mathbb{R}_+, \Omega)$.

Proof. Consider the initial value problem

$$U'(t) = F(t, U(t)) \quad \text{where} \quad U(0) = U_0.$$

The right-hand-side F satisfies the local Lipschitz condition. Therefore, the Cauchy-Lipschitz theorem ensure the local well-posedness. Then,

$$\begin{aligned} f_1(0, u_2, u_3, u_4, u_5, u_6) &= 0, \forall u_2, \dots, u_6 \in \Omega \\ f_2(u_1, 0, u_3, u_4, u_5, u_6) &= \frac{au_6 (b_h u_1 + \tilde{b}_h u_3)}{H} \geq 0, \forall u_1, u_3, \dots, u_6 \in \Omega \\ f_3(u_1, u_2, 0, u_4, u_5, u_6) &= \gamma_h u_2, \forall u_1, u_2, u_4, \dots, u_6 \in \Omega \\ f_4(u_1, u_2, u_3, 0, u_5, u_6) &= \delta_h u_2, \forall u_1, u_2, u_3, u_5, u_6 \in \Omega \\ f_5(u_1, u_2, u_3, u_4, 0, u_6) &= \alpha_m u_6 e^{-\beta_m u_6}, \forall u_1, \dots, u_4, u_6 \in \Omega \\ f_6(u_1, u_2, u_3, u_4, u_5, 0) &= \frac{ab_m u_2 u_5}{H}, \forall u_1, \dots, u_5 \in \Omega \end{aligned}$$

On one hand, note that $H' = u'_1 + u'_2 + u'_3 + u'_4 = 0$, and $u_1 + u_2 + u_3 + u_4 = H_0$. On the other hand

$$u'_5 + u'_6 = \alpha_m(u_5 + u_6)e^{-\beta_m(u_5 + u_6)} - \mu_m(u_5 + u_6),$$

or

$$M' = \alpha_m M e^{-\beta_m M} - \mu_m M.$$

If $\mu_m \geq \alpha_m$, using $e^{-\beta_m M} \leq 1$, then

$$M' \leq (\alpha_m - \mu_m)M.$$

From Grönwall's Lemma, with $\alpha_m - \mu_m \leq 0$

$$M(t) \leq e^{(\alpha_m - \mu_m)t} M_0 \leq M_0.$$

If $\alpha_m > \mu_m$, then

$$\begin{aligned} \alpha_m M e^{-\beta_m M} &= \frac{\alpha_m M}{e^{\beta_m M}} = \frac{\alpha_m M}{\sum_{n \geq 0} \frac{(\beta_m M)^n}{n!}} \\ &= \frac{\alpha_m M}{1 + \beta_m M + \frac{\beta_m^2 M^2}{2} + \frac{\beta_m^3 M^3}{6} + \dots} \\ &\leq \frac{\alpha_m}{\beta_m} \end{aligned}$$

Then $M' \leq \frac{\alpha_m}{\beta_m} - \mu_m M$ and by Gronwall's lemma $M(t) \leq e^{-\mu_m t} \left(M_0 - \frac{\alpha_m}{\beta_m \mu_m} \right) + \frac{\alpha_m}{\beta_m \mu_m} \leq M_0$.

□

2.3 Stability of equilibrium and Basic Reproduction Number $\mathcal{R}_0$

In this section, we determine the possible equilibrium points of the model and study their behavior. Let $(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*) \in \Omega$. Solving the system

$$\begin{aligned} -\frac{ab_h u_6^* u_1^*}{H_0} &= 0 \\ \frac{au_6^* (b_h u_1^* + \tilde{b}_h u_3^*)}{H_0} - \gamma_h u_2^* - \delta_h u_2^* &= 0 \\ \gamma_h u_2^* - \frac{a\tilde{b}_h u_3^* u_6^*}{H_0} &= 0 \\ \delta_h u_2^* &= 0 \\ -\frac{ab_m u_2^* u_5^*}{H_0} - \mu_m u_5^* + \alpha_m M e^{-\beta_m M} &= 0 \\ \frac{ab_m u_2^* u_5^*}{H_0} - \mu_m u_6^* &= 0 \end{aligned} \tag{7}$$

we get two disease free equilibrium $E_1 = (u_1^*, 0, u_3^*, u_4^*, 0, 0)$ and $E_2 = (u_1^*, 0, u_3^*, u_4^*, \frac{1}{\beta_m} \ln \left(\frac{\alpha_m}{\mu_m} \right), 0)$. Note that the equilibrium E_2 is biologically relevant only when $\alpha_m > \mu_m$.

Since the infected individuals are in u_2 and u_6 , then we can rewrite the system of the equations as

$$\mathcal{F} = \begin{pmatrix} \frac{au_6(b_h u_1 + \tilde{b}_h u_3)}{H_0} \\ \frac{ab_m u_2 u_5}{H_0} \end{pmatrix} \quad \mathcal{V} = \begin{pmatrix} (\gamma_h + \delta_h)u_2 \\ \mu_m u_6 \end{pmatrix}$$

where $\mathcal{F}$ is the rate of appearance of new infections in each compartment and $\mathcal{V}$ is the rate of other transitions between all compartments. Thus,

$$F = \begin{pmatrix} 0 & \frac{a(b_h u_1 + \tilde{b}_h u_3)}{H_0} \\ \frac{ab_m u_5}{H_0} & 0 \end{pmatrix}$$

and $V = \begin{pmatrix} \gamma_h + \delta_h & 0 \\ 0 & \mu_m \end{pmatrix}$ where $V^{-1} = \begin{pmatrix} \frac{1}{\gamma_h + \delta_h} & 0 \\ 0 & \frac{1}{\mu_m} \end{pmatrix}$. Therefore, the next generation matrix is

$$FV^{-1} = \begin{pmatrix} 0 & \frac{a(b_h u_1 + \tilde{b}_h u_3)}{\mu_m H_0} \\ \frac{ab_m u_5}{(\gamma_h + \delta_h)H_0} & 0 \end{pmatrix}.$$

It follows that by [15] the basic reproduction number, denoted by $\rho(FV^{-1})$, where ρ is the spectral radius, is given by

$$\rho(FV^{-1}) = \sqrt{\frac{a^2 b_m u_5 (b_h u_1 + \tilde{b}_h u_3)}{\mu_m H_0^2 (\gamma_h + \delta_h)}}.$$

Now using this eigenvalue, we determine the local stability of the equilibrium points E_1 and E_2 .

Proposition 2.2.

1. The disease free equilibrium $E_1 = (u_1^*, 0, u_3^*, u_4^*, 0, 0)$ is locally asymptotically stable.
2. If $\alpha_m > \mu_m$ and $\mathcal{R}_0 < 1$ where $\mathcal{R}_0 = \sqrt{\frac{a^2 b_m \ln\left(\frac{\alpha_m}{\mu_m}\right) (b_h u_1^* + \tilde{b}_h u_3^*)}{H_0^2 \mu_m \beta_m (\gamma_h + \delta_h)}}$, then the disease free equilibrium point $E_2 = (u_1^*, 0, u_3^*, u_4^*, \frac{1}{\beta_m} \ln\left(\frac{\alpha_m}{\mu_m}\right), 0)$ is locally asymptotically stable.

Proof. From the above eigenvalues,

$$\rho(FV^{-1}) = \sqrt{\frac{a^2 b_m(0) (\tilde{b}_h u_3^* + b_h u_1^*)}{H_0^2 \mu_m (\gamma_h + \delta_h)}} = 0$$

Therefore, the system of equation is local asymptotically stable at E_1 .

2. Similarly,

$$\mathcal{R}_0 = \sqrt{\frac{a^2 b_m u_5^* (b_h u_1^* + \tilde{b}_h u_3^*)}{\mu_m H_0^2 (\gamma_h + \delta_h)}} = \sqrt{\frac{a^2 b_m \ln\left(\frac{\alpha_m}{\mu_m}\right) (\tilde{b}_h u_3^* + b_h u_1^*)}{\mu_m H_0^2 \beta_m (\gamma_h + \delta_h)}}.$$

□

The basic reproduction number $\mathcal{R}_0$ has a biological meaning when $\alpha_m > \mu_m$. It means that the average number of new infected humans is proportional to the proportion $\frac{u_5^*}{H_0}$ of susceptible mosquitoes among the human population. The terms $\frac{u_1^*}{H_0}$, and $\frac{u_3^*}{H_0}$ proportion of primary and secondary susceptible humans respectively. The terms $\frac{ab_h}{\mu_m(\gamma_h + \delta_h)}$, and $\frac{a\tilde{b}_h}{\mu_m(\gamma_h + \delta_h)}$ represent the transmission rate due by biting during the infection period $1/(\gamma_h + \delta_h)$ and mosquitoes life expectancy $1/\mu_m$.

Remark 2.3. Local stability can be proved using the Jacobian matrix defined as

$$J = \begin{pmatrix} \frac{-ab_h u_6}{H_0} & 0 & 0 & 0 & 0 & \frac{-ab_h u_1}{H_0} \\ \frac{ab_h u_6}{H_0} & -\gamma_h - \delta_h & \frac{a\tilde{b}_h u_6}{H_0} & 0 & 0 & \frac{ab_h u_1 + a\tilde{b}_h u_3}{H_0} \\ 0 & \gamma_h & \frac{-ab_h u_6}{H_0} & 0 & 0 & \frac{-ab_h u_3}{H_0} \\ 0 & \delta_h & 0 & 0 & 0 & 0 \\ 0 & \frac{-ab_m u_5}{H_0} & 0 & 0 & \frac{-ab_m u_2}{H_0} - \mu_m + \alpha_m e^{-\beta_m M} (1 - \beta_m M) & \alpha_m e^{-\beta_m M} (1 - \beta_m M) \\ 0 & \frac{ab_m u_5}{H_0} & 0 & 0 & \frac{ab_m u_2}{H_0} & -\mu_m \end{pmatrix}$$

Concerning the disease free equilibrium $E_1 = (u_1^*, 0, u_3^*, u_4^*, 0, 0)$, we get as eigenvalues

$$\lambda_1 = 0 \text{ with multiplicity } 3$$

$$\lambda_2 = -\gamma_h - \delta_h$$

$$\lambda_3 = -\mu_m$$

$$\lambda_4 = -\mu_m + \alpha_m$$

If $\alpha_m - \mu_m \leq 0$, all the eigenvalues are negative. Implying further that the system of equation is asymptotically stable at the equilibrium E_1 .

For the second equilibrium $E_2 = (u_1^*, 0, u_3^*, u_4^*, \frac{1}{\beta_m} \ln \left(\frac{\alpha_m}{\mu_m} \right), 0)$, the eigenvalues are

$$\lambda = 0 \quad \text{with multiplicity 3}$$

$$\lambda = -\mu_m \ln \left(\frac{\alpha_m}{\mu_m} \right)$$

$$\lambda = -\frac{\gamma_h + \delta_h + \mu_m}{2} \pm \sqrt{\frac{(\gamma_h + \delta_h + \mu_m)^2 - 4 \left(\mu_m(\gamma_h + \delta_h) - \frac{ab_m \ln \left(\frac{\alpha_m}{\mu_m} \right) (ab_h u_1^* + a\tilde{b}_h u_3^*)}{H_0^2 \beta_m} \right)}{2}}$$

which are negative if $\alpha_m > \mu_m$ and $\mathcal{R}_0 > 1$.

Theorem 2.4.

1. If $\alpha_m < \mu_m$, then E_1 is globally asymptotically stable.
2. If $\alpha_m > \mu_m$ and $\mathcal{R}_0 > 1$, then E_2 is globally asymptotically stable.

Proof. From equation (4), we can deduce that u_4 is increasing. Since u_4 is bounded by H_0 , u_4 has a limit u_4^* as $t \rightarrow +\infty$. Thus, integrating equation (4) gives

$$u_4(t) - u_4(0) = \delta_h \int_0^t u_2(s) ds.$$

Thus

$$u_4^* - u_4(0) = \delta_h \int_0^\infty u_2(s) ds$$

which is finite. Implying further that $u_2(s) \rightarrow 0$ as $s \rightarrow +\infty$. Now, adding equation (5) and (6) gives us

$$u_5' + u_6' = M' = g(M) = \alpha_m M e^{-\beta_m M} - \mu_m M.$$

As in Theorem 2.1, if $\alpha_m < \mu_m$, then $M(t) \rightarrow 0$ as $t \rightarrow +\infty$. Thus, by positivity of the solution u_5 and u_6 goes to 0 as $t \rightarrow +\infty$. From equation (1) $u_1' = -\frac{ab_h u_6 u_1}{H_0} \leq 0$, the function u_1 is decreasing non-negative function, bounded by H_0 . Thus, as $t \rightarrow +\infty$, $u_1 \rightarrow u_1^*$. The solution of equation (3) $u_3' + \frac{a\tilde{b}_h u_6 u_3}{H_0} = \gamma_h u_2$, can be written as

$$u_3(t) = E(t)u_3(0) + \int_0^t E(t-s)\gamma_h u_2(s) ds$$

with $E(t) = e^{-\frac{a\tilde{b}_h}{H_0} \int_0^t u_6(s) ds}$. Since, for all $t \geq 0$, $0 \leq u_2(t)$, $u_3(t) \leq H_0$, $0 \leq u_6(t) \leq M_0$, then $u_2 \rightarrow 0$, $u_3 \rightarrow u_3^*$ when $t \rightarrow +\infty$.

When $\alpha_m \geq \mu_m$, let us denote $M^* = \frac{1}{\beta_m} \ln \left(\frac{\alpha_m}{\mu_m} \right)$. Since $M'(t) = (\alpha_m e^{-\beta_m M} - \mu_m)M$, if $M(t) < M^*$, then M is increasing and bounded by above, while if $M(t) > M^*$, then M is decreasing and bounded by below. In particular, $M(t)$ has a limit when $t \rightarrow +\infty$. Using now the local asymptotic stability with $\mathcal{R}_0 < 1$, this limit is equal to M^* . □

3 Comparison of control strategies

In this section, we describe three control strategies in preventing or reducing dengue transmission.

3.1 Vaccination

To account for vaccine in the model, let us consider the following mathematical model:

$$\begin{aligned}
 u_1'(t) &= -\frac{ab_h u_6(t)u_1(t)}{H_0} - v_1 u_1(t) \\
 u_2'(t) &= \frac{au_6(t) \left(b_h u_1(t) + \tilde{b}_h u_3(t) \right)}{H_0} - \gamma_h u_2(t) - \delta_h u_2(t) \\
 u_3'(t) &= \gamma_h u_2(t) - \frac{\tilde{a}\tilde{b}_h u_3(t)u_6(t)}{H_0} - v_3 u_3(t) \\
 u_4'(t) &= \delta_h u_2(t) \\
 u_5'(t) &= -\frac{ab_m u_2(t)u_5(t)}{H_0} - \mu_m u_5(t) + \alpha_m M e^{-\beta_m M} \\
 u_6'(t) &= \frac{ab_m u_2(t)u_5(t)}{H_0} - \mu_m u_6(t).
 \end{aligned} \tag{8}$$

We distinguish the vaccination given to the primary susceptible human population ($v_1 u_1$), and the vaccination given to the secondary susceptible human ($v_3 u_3$). The total immunity is given by $T_h'(t) = v_1 u_1(t) + v_3 u_3(t)$.

Note that there exists a unique global in time solution $(u_1, u_2, u_3, u_4, u_5, u_6)$ in $\mathcal{C}(\mathbb{R}_+, \mathbb{R}_+)^6$. And the system of equations (8) admits two equilibria $E_{1,vac} = (0, 0, 0, u_4^*, 0, 0)$ and $E_{2,vac} = (0, 0, 0, u_4^*, \frac{1}{\beta_m} \ln(\frac{\alpha_m}{\mu_m}), 0)$.

The next generation matrix does not change, and the basic reproduction number is $\mathcal{R}_{vac} = 0$. Therefore, we have the following theorem.

Theorem 3.1. 1. If $\alpha_m < \mu_m$, then $E_{1,vac}$ is globally asymptotically stable.

2. If $\alpha_m > \mu_m$, then $E_{2,vac}$ is globally asymptotically stable.

Proof. The proof is similar to the proof of Theorem 2.4 by replacing $\frac{ab_h u_6}{H_0}$ by $\left(\frac{ab_h u_6}{H_0} + v_1 \right)$ and $\frac{\tilde{a}\tilde{b}_h u_6}{H_0}$ by $\left(\frac{\tilde{a}\tilde{b}_h u_6}{H_0} + v_3 \right)$. $\square$

3.2 Vector Control

Vector control consists in limiting the vectors that transmit disease. The most frequent type of vector control uses various strategies such as habitat and environmental control, reducing vector contact, chemical control, and biological control. To include vector control, let us consider a mathematical model below:

$$\begin{aligned}
 u_1'(t) &= -\frac{ab_h u_6(t)u_1(t)}{H_0} \\
 u_2'(t) &= \frac{au_6(t) \left(b_h u_1(t) + \tilde{b}_h u_3(t) \right)}{H_0} - \gamma_h u_2(t) - \delta_h u_2(t) \\
 u_3'(t) &= \gamma_h u_2(t) - \frac{\tilde{a}\tilde{b}_h u_3(t)u_6(t)}{H_0} \\
 u_4'(t) &= \delta_h u_2(t) \\
 u_5'(t) &= -\frac{ab_m u_2(t)u_5(t)}{H_0} - \mu_m u_5(t) + \alpha_m M e^{-\beta_m M} - v_m u_5(t) \\
 u_6'(t) &= \frac{ab_m u_2(t)u_5(t)}{H_0} - \mu_m u_6(t) - v_m u_6(t)
 \end{aligned} \tag{9}$$

where $v_m u_5$ is the vector control given to the susceptible mosquito population, and $v_m u_6$ is the vector control to infectious mosquito. The total controlled mosquito is given by $T_m'(t) = v_m(u_5(t) + u_6(t))$.

Again, there exists a unique global in time solution $(u_1, u_2, u_3, u_4, u_5, u_6)$ in $\mathcal{C}(\mathbb{R}_+, \mathbb{R}_+)^6$, and the system admits two equilibria $E_{1,vec} = (u_1^*, 0, u_3^*, u_4^*, 0, 0)$ and $E_{2,vec} = \left(u_1^*, 0, u_3^*, u_4^*, \frac{1}{\beta_m} \ln \left(\frac{\alpha_m}{v_m + \mu_m} \right), 0\right)$.

Here the basic reproduction number is

$$\mathcal{R}_{vec} = \sqrt{\frac{a^2 b_m \frac{1}{\beta_m} \ln \left(\frac{\alpha_m}{\mu_m + v_m} \right) (\tilde{b}_h u_3^* + b_h u_1^*)}{H_0^2 (\mu_m + v_m) (\gamma_h + \delta_h)}}.$$

Theorem 3.2. 1. If $\alpha_m < \mu_m + v_m$, then $E_{1,vec}$ is globally asymptotically stable.
2. If $\alpha_m > \mu_m + v_m$ and $\mathcal{R}_{vec} > 1$, then $E_{2,vec}$ is globally asymptotically stable.

3.3 Vaccination and Vector Control

When the dengue vaccination and the vector control method are combined, we have:

$$\begin{aligned} u_1'(t) &= -\frac{ab_h u_6(t) u_1(t)}{H_0} - v_1 u_1(t) \\ u_2'(t) &= \frac{au_6(t) (b_h u_1(t) + \tilde{b}_h u_3(t))}{H_0} - \gamma_h u_2(t) - \delta_h u_2(t) \\ u_3'(t) &= \gamma_h u_2(t) - \frac{a\tilde{b}_h u_3(t) u_6(t)}{H_0} - v_3 u_3(t) \\ u_4'(t) &= \delta_h u_2(t) \\ u_5'(t) &= -\frac{ab_m u_2(t) u_5(t)}{H_0} - \mu_m u_5(t) + \alpha_m M e^{-\beta_m M} - v_m u_5(t) \\ u_6'(t) &= \frac{ab_m u_2(t) u_5(t)}{H_0} - \mu_m u_6(t) - v_m u_6(t) \end{aligned} \quad (10)$$

where total human immunity is given by $T'_h(t) = v_1 u_1(t) + v_3 u_3(t)$ and total vector control is given by $T'_m(t) = v_m u_5(t) + v_m u_6(t)$.

There exists a unique global in time solution $(u_1, u_2, u_3, u_4, u_5, u_6)$ in $\mathcal{C}(\mathbb{R}_+, \mathbb{R}_+)^6$, and the system admits two equilibria $E_{1,both} = (0, 0, 0, u_4^*, 0, 0)$ and $E_{2,both} = \left(0, 0, 0, u_4^*, \frac{1}{\beta_m} \ln \left(\frac{\alpha_m}{\mu_m + v_m} \right), 0\right)$.

Theorem 3.3. 1. If $\alpha_m < \mu_m + v_m$, then $E_{1,both}$ is globally asymptotically stable.
2. If $\alpha_m > \mu_m + v_m$, then $E_{2,both}$ is globally asymptotically stable.

4 Optimal Control Problem

4.1 Minimizing Infected Humans by Optimal Vaccination and Vector Control

Assume that both control inputs are piecewise continuous functions that take its values in a positively bounded set $W = [0, w_H]^2 \times [0, w_M]^2$. Thus we consider the objective function

$$\mathcal{J}(w_1, w_3, w_m) = \int_0^T u_2(t) + \frac{1}{2} \left(A_1 w_1^2(t) + A_3 w_3^2(t) + A_m w_m^2(t) \right) dt$$

subject to

$$\begin{aligned}
 u_1'(t) &= -\frac{ab_h u_6(t) u_1(t)}{H_0} - w_1(t) u_1(t) \\
 u_2'(t) &= \frac{au_6(t) (b_h u_1(t) + \tilde{b}_h u_3(t))}{H_0} - \gamma_h u_2(t) - \delta_h u_2(t) \\
 u_3'(t) &= \gamma_h u_2(t) - \frac{a\tilde{b}_h u_3(t) u_6(t)}{H_0} - w_3(t) u_3(t) \\
 u_4'(t) &= \delta_h u_2(t) \\
 u_5'(t) &= -\frac{ab_m u_2(t) u_5(t)}{H_0} + g(M(t)) - \mu_m u_5(t) - w_m(t) u_5(t) \\
 u_6'(t) &= \frac{ab_m u_2(t) u_5(t)}{H_0} - \mu_m u_6(t) - w_m(t) u_6(t)
 \end{aligned} \tag{11}$$

for $t \in [0, T]$, with $0 \leq w_1, w_3 \leq w_H$, $0 \leq w_m \leq w_M$ and $w = (w_1, w_3, w_m)$. The variables A_j are the positive weights associated with the control variables w_j , $j = 1, 3, m$, respectively.

Lemma 4.1. *There exists an optimal control $w^* = (w_1^*(t), w_3^*(t), w_m^*(t))$ such that*

$$\mathcal{J}(w_1^*, w_3^*, w_m^*) = \min_{w \in W} \mathcal{J}(w_1, w_3, w_m)$$

under the constraint $(u_1, u_2, u_3, u_4, u_5, u_6)$ is a solution of (11).

Proof. Since all control inputs $w_1(t)$, $w_3(t)$ and $w_m(t)$ are piecewise continuous functions that takes its values in a positively bounded set W and $u_2(t)$ is continuous, the corresponding set of controls and the state variables is nonempty, closed and convex on W . The objective function is convex and coercive. $\square$

Pontryagin's maximum principle is used to find the best possible control for taking a dynamical system from one state to another. It states that it is necessary for any optimal control along with the optimal state trajectory to solve the so-called Hamiltonian system [10]. We state the lemma below.

Lemma 4.2. *There exist the adjoint variables λ_i , $i = 1, 2, \dots, 6$ of the system (11) that satisfy the following backward in time system of ordinary differential equations:*

$$\begin{aligned}
 -\frac{d\lambda_1}{dt} &= \lambda_1 \left(\frac{-ab_h u_6}{H_0} - w_1 \right) + \lambda_2 \frac{ab_h u_6}{H_0} \\
 -\frac{d\lambda_2}{dt} &= 1 + \lambda_2 (-\gamma_h - \delta_h) + \lambda_3 \gamma_h + \lambda_4 \delta_h - \lambda_5 \frac{ab_m u_5}{H_0} + \lambda_6 \frac{ab_m u_5}{H_0} \\
 -\frac{d\lambda_3}{dt} &= \lambda_2 \frac{a\tilde{b}_h u_6}{H_0} + \lambda_3 \left(\frac{-a\tilde{b}_h u_6}{H_0} - w_3 \right) \\
 -\frac{d\lambda_4}{dt} &= 0 \\
 -\frac{d\lambda_5}{dt} &= \lambda_5 \left(\frac{-ab_m u_2}{H_0} + \frac{\partial g}{\partial u_5} \right) - \lambda_5 (\mu_m + w_m) + \lambda_6 \frac{ab_m u_2}{H_0} \\
 -\frac{d\lambda_6}{dt} &= -\lambda_1 \frac{ab_h u_1}{H_0} + \lambda_2 \frac{ab_h u_1 + a\tilde{b}_h u_3}{H_0} - \lambda_3 \frac{a\tilde{b}_h u_3}{H_0} + \lambda_5 \frac{\partial g}{\partial u_6} - \lambda_6 (\mu_m + w_m)
 \end{aligned}$$

with the transversality condition $\lambda(T) = 0$.

Proof. Using the Hamiltonian for (11), we have

$$\begin{aligned}
 \mathcal{H} &= \mathcal{L}(w_1, w_3, w_m) + \lambda_1(t)u'_1(t) + \lambda_2(t)u'_2(t) + \lambda_3(t)u'_3(t) + \lambda_4(t)u'_4(t) + \lambda_5(t)u'_5(t) + \lambda_6(t)u'_6(t) \\
 &= \frac{1}{2} \left(u_2^2 + A_1 w_1^2 + A_3 w_3^2 + A_m w_m^2 \right) \\
 &\quad + \lambda_1 \left(-\frac{ab_h u_6 u_1}{H_0} - w_1 u_1 \right) + \lambda_3 \left(\gamma_h u_2 - \frac{a\tilde{b}_h u_3 u_6}{H_0} - w_3 u_3 \right) \\
 &\quad + \lambda_2 \left(\frac{au_6 (b_h u_1 + \tilde{b}_h u_3)}{H_0} - \gamma_h u_2 - \delta_h u_2 \right) + \lambda_4 (\delta_h u_2) \\
 &\quad + \lambda_5 \left(-\frac{ab_m u_2 u_5}{H_0} + g(M) - \mu_m u_5 - w_m u_5 \right) \\
 &\quad + \lambda_6 \left(\frac{ab_m u_2 u_5}{H_0} - \mu_m u_6 - w_m u_6 \right). \tag{12}
 \end{aligned}$$

Therefore, finding the partial derivatives of $\mathcal{H}$ with respect to u_i 's, $i = 1, 2, \dots, 6$, we have

$$\begin{aligned}
 \frac{\partial \mathcal{H}}{\partial u_1} &= \lambda_1 \left(-\frac{ab_h u_6}{H_0} - w_1 \right) + \lambda_2 \frac{ab_h u_6}{H_0} \\
 \frac{\partial \mathcal{H}}{\partial u_2} &= 1 + \lambda_2 (-\gamma_h - \delta_h) + \lambda_3 \gamma_h + \lambda_4 \delta_h - \lambda_5 \frac{ab_m u_5}{H_0} + \lambda_6 \frac{ab_m u_5}{H_0} \\
 \frac{\partial \mathcal{H}}{\partial u_3} &= \lambda_2 \frac{a\tilde{b}_h u_6}{H_0} + \lambda_3 \left(-\frac{a\tilde{b}_h u_6}{H_0} - w_3 \right) \\
 \frac{\partial \mathcal{H}}{\partial u_4} &= 0 \\
 \frac{\partial \mathcal{H}}{\partial u_5} &= \lambda_5 \left(-\frac{ab_m u_2}{H_0} + \frac{\partial g}{\partial u_5} \right) - \lambda_5 (\mu_m + w_m) + \lambda_6 \frac{ab_m u_2}{H_0} \\
 \frac{\partial \mathcal{H}}{\partial u_6} &= -\lambda_1 \frac{ab_h u_1}{H_0} + \lambda_2 \frac{ab_h u_1 + a\tilde{b}_h u_3}{H_0} - \lambda_3 \frac{a\tilde{b}_h u_3}{H_0} + \lambda_5 \frac{\partial g}{\partial u_6} - \lambda_6 (\mu_m + w_m).
 \end{aligned}$$

Then the adjoint system is defined by $\frac{d\lambda_i}{dt} = -\frac{\partial \mathcal{H}}{\partial u_i}$ for $i = 1, 2, \dots, 6$. $\square$

Theorem 4.3. The optimal control variables are given by

$$\begin{aligned}
 w_1^*(t) &= \max \left(0, \min \left(\frac{\lambda_1 u_1}{A_1}, w_H \right) \right) \\
 w_3^*(t) &= \max \left(0, \min \left(\frac{\lambda_3 u_3}{A_3}, w_H \right) \right) \\
 w_m^*(t) &= \max \left(0, \min \left(\frac{\lambda_5 u_5 + \lambda_6 u_6}{A_m}, w_M \right) \right)
 \end{aligned}$$

Proof. By the Pontryagin maximum principle, the optimal control w^* minimizes, at each instant t , the Hamiltonian given by (12). We have

$$\frac{\partial H}{\partial w_j} = 0, \quad \text{for all } j = 1, 3, m \text{ at } w_j = w_j^*.$$

Therefore, we get

$$\frac{\partial \mathcal{H}}{\partial w_1} = A_1 w_1 - \lambda_1 u_1, \quad \frac{\partial \mathcal{H}}{\partial w_3} = A_3 w_3 - \lambda_3 u_3, \quad \frac{\partial \mathcal{H}}{\partial w_m} = A_m w_m - \lambda_5 u_5 - \lambda_6 u_6,$$

and

$$w_1 = \frac{\lambda_1 u_1}{A_1}, \quad w_3 = \frac{\lambda_3 u_3}{A_3}, \quad w_m = \frac{\lambda_5 u_5 + \lambda_6 u_6}{A_m}.$$

$\square$

4.2 Numerical Simulation of Optimal Control

Numerical simulations show the difference in minimizing the infected human during the dengue outbreak between the three methods: vaccination, vector control, and the combination of the vaccination and vector control.

Table 1: Parameter values used in the numerical simulations.

Symbol	Description	Values
a	number of human beaten per mosquito	1
b_h	probability of becoming infected	0.75
$\tilde{b}_h$	probability of becoming infected again	0.375
α_h	growth rate of human	0.0045
γ_h	recovery rate of human from first infection	0.328833
δ_h	recovery rate of human from the second infection	0.1666
b_m	probability of becoming infectious	0.375
μ_m	death rate of mosquito	0.02941
α_m	growth rate of mosquito	0.025

The parameters are presented in Table 1, which is taken from [3]. Notice that $\alpha_m < \mu_m$, by Theorem 2.4 the global stability corresponds to E_1 . Here E_2 is biologically not meaningful in this situation. The author estimated some from Indonesia, where environmental conditions are similar to the Philippines. The control weights A_1 and A_3 are the efforts in vaccinating the human population. In contrast, the control weights A_m is the effort to eliminate the mosquito population by means of administering insecticides. Since primary susceptible humans are readily available in the population compared to the secondary susceptible humans, the efforts used in vaccinating them would be less than the effort exerted in vaccinating the secondary susceptible. Thus, A_3 is set higher than A_1 . While insecticide administration in susceptible mosquitoes and infected mosquitoes uses the same effort and achieves a similar result. Hence, we initially set the control weights as $A_1 = 0.1$, $A_3 = 1$ and $A_m = 1$. Note that the values of A_1 , A_3 , A_m do not change the convergence of optimal control.

The optimality of the system is numerically solved using Algorithm 1 with $\epsilon = 0.01$.

Algorithm 1 Computation of optimal control of dengue-dengvaxia

Given $U^0 = (10^4, 0, 0, 0, 10^5, 10^3)$ as initial datum, a final time $T > 0$ and a tolerance $\epsilon > 0$.

Let w_1^0, w_2^0, w_m^0 randomly chosen following $\mathcal{N}(0, 1)$.

while $\|\nabla \mathcal{H}(w^n, U^n, \lambda^n)\| > \epsilon$ **do**,

 solve the forward system u^n ,

 solve the backward system λ^n ,

 update w^n

 solve the gradient $\nabla \mathcal{H}(w^n, U^n, \lambda^n)$

$w^* = w^n$.

Figure 2 shows in minimizing the infected human that the combination of Dengvaxia and vector control is the most effective method. It would only take 30 days to reach equilibrium, resulting in the total elimination of infected humans with a maximum of 12.55% (1,255) infected humans over time. Nevertheless, vector control stands out if we compare only the vaccination and vector control method. It would only take 34 days with a maximum population of 19.68% (1,968) infected humans for vector control to eliminate infected humans.

Figure 2: Behaviour of infected humans I_h with respect to time without control (red), for the optimal control related to the vaccination only (green), related to the vector only (orange), and with both control (blue). Cyan curve corresponds to optimal control of vaccination of secondary humans only.

In comparison, vaccination takes 45 days, with 18.42% (1,842) infected humans. Without control, infected humans would slowly decrease after reaching 60.07% (6,007) but would never annihilate. Vaccinating secondary humans would only take 48 days to reach equilibrium with a maximum of 54.94% (5,494) infected humans over time.

Figure 3: Behaviour of (A) human compartment and (B) mosquito compartment with respect to time without control (red), for the optimal control related to the vaccination only (green), related to the vector only (orange), and with both control (blue).

Figure 3 shows no significant difference between the three methods concerning the primary and secondary susceptibles to reach its equilibrium point. It takes seven and a half days for vaccination and 14 days to combine vaccination and vector control to reach zero primary susceptible individuals. Moreover, it takes 42 days for vaccination and 30 days for the combination to reach zero secondary susceptible individuals. For vector control, it takes 20 days to reach an equilibrium of 53.36% (5336) primary susceptible humans and 34 days to reach 30.15% (3015) secondary susceptible humans.

Note that in the human compartment, the total immunity to dengue by means of implementing the Dengvaxia vaccine is denoted by T_h which is given by $T_h(t) = w_1(t)u_1(t) + w_3(t)u_3(t)$. Thus, a healthy human com-

bines immune human T_h , primary susceptible u_1 , secondary susceptible u_3 , and the recovered u_4 humans. The figure shows that the combination of vaccination and vector control is the best method in maximizing the healthy human population. It only takes 26 days to combine vaccination and vector control methods to reach the equilibrium of healthy humans. Its minimum population is 8.73% (8,734) on day 1.8.

In contrast, there is no significant difference in the vector and vaccination method alone in the healthy human population. The vector method takes 29 days to reach its equilibrium with 8.02% (8,021) minimum population on 2.8 days. The vaccination required 39 days to reach an equilibrium with 8.16% (8,157) minimum population on 2.5 days. Without any control strategies applied to the healthy human population, it requires a much higher time to reach its equilibrium with 4% (4,000) minimum population.

For the recovered human compartment, the figure shows that the human population would eventually recover through time without control strategies applied to the variables. It supports that dengue infection lasts only three to seven days following the infectious mosquito bite, and a spontaneous, full health recovery follows. However, comparing the three control methods, the combination of vaccination and vector control methods stands out. It only requires 26 days to reach its equilibrium at 0.79% (787) recovered human population. At the same time, there is no significant difference between vaccination alone and vector control alone. Both require 32 days to reach its equilibrium at 1.59% (1,590) and 1.65% (1,646) recovered human, respectively.

Now, minimizing the susceptible mosquito population, no control applied to the variables is better than vaccination. It decreases faster with 0.56% (556) minimum susceptible mosquito population while vaccination decreases slower with 3.69% (3,692) minimum population at the end of time. Nevertheless, the vector control method and the combination of vaccination and vector control are the better methods for controlling the mosquito population. They annihilate the susceptible mosquito population.

Minimizing the infected mosquito, either vector control alone or combining vaccination and vector control is the best method. There is no significant difference between the two. They both require minimum time for the infected mosquito to reach zero population and with only 2.6% (2596) and 2.52% (2521) maximum population for the vector control only and the combination, respectively. However, vaccination is better compared to the one without control. The infected mosquito has a 58.09% (58,092) maximum population without applying a control strategy, while the vaccination has a 22% (22,006) maximum population.

Now, let us show the controlled variable's behavior by comparing the vaccination, vector control only, and the combination of vaccination and vector control.

Figure 4: Optimal control of the (A) primary susceptible and (B) secondary susceptible human compartment using vaccination only versus the combination of both control strategies. Optimal control of (C) mosquitoes compartment using vector control only versus the combination of both control strategies. Cyan curve represents optimal control of vaccination of secondary humans only

Figure 4 shows that concerning vaccination only, vaccinating the primary susceptible human population requires a shorter time compared to the secondary susceptible human. It takes ten days and 40 days to vaccinate primary and secondary susceptible human populations, respectively. Nevertheless, applying both control strategies takes only approximately 20–22 days. While minimizing the mosquito population, the vector control method is better than combining the two strategies. It takes approximately 15–18 days to administer insecticide to the mosquito population while applying both control strategies takes 22–24 days.

5 Conclusion

Following Ross' model, we build a mathematical model for dengue where secondary susceptible individuals partake in the infection. As proposed by Sanofi, the dengue vaccine is recommended to individuals who have been infected by one serotype of dengue [16]. In our study, we have shown that vaccinating secondary susceptible humans only is not ideal. It requires constant effort and takes a long time to vaccinate them, as observed in Figure 2 (cyan curve) and Figure 4. Instead, it is better to vaccinate the primary susceptible humans. However, since safe vaccines for primary susceptible humans do not exist to date, the application of vector control to minimize infected humans is a better counter-strategy.

Our results show that vector control is better than vaccination to maximize the healthy human population in a short period. Thus, using cyclopoid copepods (*Mesocyclops spp.*) or the releasing of mosquitoes modified to carry a Wolbachia bacteria is better than vaccination. However, further study with good design, data quality, and appropriate statistics is needed for this.

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